

PATENT SPECIFICATION

(11) 1 484 663

1 484 663

- (21) Application No. 6275/75 (22) Filed 14 Feb. 1975
 (31) Convention Application No. 442 990
 (32) Filed 15 Feb. 1974 in
 (33) United States of America (US)
 (44) Complete Specification published 1 Sept. 1977
 (51) INT CL² A24B 15/00
 (52) Index at acceptance A2C 20H1



(54) THE TREATMENT OF SMOKING MATERIAL

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company, of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to the treatment of smoking material. More particularly, the invention is concerned with compositions based on tobacco and a process for the manufacture thereof. The invention is also concerned with a method for the reduction of nitrogen dioxide content in tobacco smoke.

The compositions provided by the present invention comprise tobacco and, dispersed therein, a substance selected from an about equimolar mixture of ascorbic acid and a pharmaceutically acceptable salt thereof, an about equimolar mixture of erythorbic acid and a pharmaceutically acceptable salt thereof and mixtures thereof.

The toxic effects of tobacco smoke, which had been suspect for many years, have now been firmly established by an overwhelming quantity of scientific evidence. Among the various harmful substances which have been shown to be present in tobacco smoke are the various oxides of nitrogen. Of those nitrogen oxides normally present in tobacco smoke, nitrogen dioxide is the most toxic and most irritating. While the views of experts in the field are at a variance, it is estimated that as much as 50% of the nitrogen oxide content of tobacco smoke is nitrogen dioxide. The total nitrogen oxide content of tobacco smoke has been reported to range from about 145 ppm to 1000 ppm.

In addition to the irritating and toxic properties of nitrogen dioxide *per se* in tobacco smoke, it has recently been shown that nitrogen dioxide and certain other oxides of nitrogen can form nitrosating intermediates which, in turn, can react with susceptible organic amines in the unburned tobacco to form nitrosamines. It is reported in the literature that up to 140

ng of N-dimethylnitrosamine can be present in the smoke of one cigarette. The nitrosamine content in the smoke from different types of tobacco can vary from practically none up to 140 ng/cigarette. The amount of nitrosamines present in the smoke of a given type of tobacco is influenced by a number of variables such as, for example, the amount of nitrogen-containing fertiliser used in growing the tobacco plants. N-Dimethylnitrosamine is a highly toxic substance and is recognised as a potent carcinogen in animal experiments even at low levels of administration. It is therefore readily apparent that means to effectively reduce the nitrogen dioxide content of tobacco smoke would be of considerable benefit to those individuals who smoke tobacco in some form. Such a means is provided in accordance with the present invention.

The effect of smoking on the ascorbic acid content of the human body, as well as the benefit heavy smokers might possibly derive from the ingestion of large amounts of ascorbic acid, have been the subject of a number of reports in the literature. Thus, for example, the substantial depletion of vitamin C in the body, caused by smoking, is known and some experts recommend the ingestion of large amounts of ascorbic acid by heavy smokers for the prevention and treatment of what is termed "smoker's scurvy". This depletion of vitamin C in the body of heavy smokers has been substantiated by numerous others working in the field. These workers have also recommended that heavy smokers consume an abundance of vitamin C to prevent development of a deficiency thereof. These findings and recommendations are directed to the alleviation of one of the harmful effects of heavy smoking in the body, but do not effect the prevention of the formation of nitrosamines or oxides of nitrogen and their presence in the inhaled tobacco smoke.

French Patent No. 932,560 discloses a device such as cigarette paper, straw-like structure, holder, mouthpiece or similar article with which the smoke comes in contact as it is being inhaled. The device, which may or

may not be burned with tobacco, is of a fibrous nature and is either impregnated or covered with a "metabolite" which is stated as being a substance which can interact with normal cell metabolism such as, for example, vitamins including ascorbic acid, enzymes, co-enzymes and the like. The stated object in having such substances impregnated in or coated on such a device is that the device facilitates the mixing of these metabolites with the smoke in appreciable quantities, thereby causing them to be inhaled with the smoke. The patent states that the presence of one or more of these metabolites in appreciable quantities in the smoke increases the tolerance of the user to "the toxic products (nicotine)" contained in the smoke. In operation, the metabolites contained in or coated on the device are stated as being progressively volatilised by the heat of combustion and are mixed with and consumed with the smoke.

The stated object of the device disclosed and claimed in this French patent is to increase the tolerance of the smoker to the toxic products (nicotine) in the smoke. The teachings of the French patent, therefore, parallel those concerning the systemic administration of ascorbic acid to offset the deleterious effects of smoking, in that all are concerned with attempting to minimise such effects after the smoke has been inhaled.

It has been found in accordance with the present invention that the amounts of at least one toxic substance, i.e. nitrogen dioxide, which is normally consumed with tobacco smoke, can be sharply reduced before the smoke is inhaled.

The present invention is based on the discovery that the nitrogen dioxide content of tobacco smoke is markedly reduced as it is being drawn through uncombusted tobacco of a composition of the invention.

According to the present invention there is provided a composition comprising tobacco and, dispersed therein, a substance selected from a substantially equimolar mixture of ascorbic acid and a pharmaceutically acceptable salt thereof, a substantially equimolar mixture of erythorbic acid and a pharmaceutically acceptable salt thereof and mixtures thereof.

Where tobacco is treated with these substances in accordance with the invention, the reduction in nitrogen dioxide content of the smoke in turn further causes a reduction in the formation of nitrosamines which can be inhaled with the smoke. The formation of nitrosamines has been shown to occur as a result of reaction of nitrogen dioxide in the smoke with susceptible organic amines in the uncombusted tobacco. Thus, the effects achieved according to the invention are most important since nitrogen dioxide is the most toxic and irritating of the nitrogen oxides normally present in the smoke and at least one

nitrosamine, i.e. N-dimethylnitrosamine, is a recognised carcinogen.

The present invention thus further provides a method for the reduction of nitrogen dioxide content in tobacco smoke, which method comprises passing said smoke through uncombusted tobacco having dispersed therein an effective amount of a substance selected from a substantially equimolar mixture of ascorbic acid and a pharmaceutically acceptable salt thereof, a substantially equimolar mixture of erythorbic acid and a pharmaceutically acceptable salt thereof and mixtures thereof.

The compositions of the present invention can be prepared according to methods known *per se*; for example, by dispersing throughout the tobacco an effective amount of a substance selected from a substantially equimolar mixture of ascorbic acid and a pharmaceutically acceptable salt thereof, a substantially equimolar mixture of erythorbic acid and a pharmaceutically acceptable salt thereof and mixtures thereof.

The amount of such substances used in accordance with the invention will vary over a wide range depending on such criteria as the "tar" content of the tobacco and, more particularly, on the organic nitrogen content thereof. Generally, treatment of tobacco with any amount of the specified substances will cause some reduction in the nitrogen dioxide content of the smoke. As a practical matter, it has been found that an effective amount of such substances constitutes from 0.1% by weight to 10% by weight of the tobacco on a dry basis. In a more preferred embodiment, tobacco is treated with from 1% by weight to 4% by weight, on a dry basis, of one or more of the substances mentioned earlier. As the average cigarette contains approximately one gram of tobacco, the foregoing preferred percentage range represents from 10 mg to 40 mg of the substances per cigarette.

It is recognised that the tar and impurity content of tobacco smoke is materially increased as the tobacco in e.g. a cigarette or cigar is consumed. Therefore, it will be appreciated that treatment of tobacco in accordance with the present invention may not have an appreciable effect on the last two or three inhalations of smoke. Thus, in order to achieve the full benefits of the present invention, smoking of such as a cigarette or cigar containing treated tobacco should be discontinued while a reasonable amount remains unburned. It has been demonstrated by taste tests on human volunteers that the amount of the substances to be dispersed in the tobacco has no detectable adverse effect on the taste of the smoke.

It is believed that the substances used to treat tobacco in accordance with the present invention react with nitrogen dioxide to form nitric oxide and water. This so-called "trap-

ping" of the nitrogen dioxide, in addition to removing a substantial amount thereof from the smoke taken into the lungs, acts to competitively inhibit the formation of carcinogenic nitrosamines by reaction of nitrogen dioxide with amines in the unburned tobacco. In one series of tests, it has been demonstrated that smoke from cigarettes prepared from compositions in accordance with the present invention and comprising a mixture of about 12 mg of equal parts of ascorbic acid and sodium ascorbate per cigarette, contains about one-third of the nitrogen dioxide content of untreated controls utilising a slow puff test and about one-half the nitrogen dioxide content of controls using a fast puff test. It has also been demonstrated, using cigarettes containing approximately 25 mg of an equimolar mixture of ascorbic acid and sodium ascorbate per cigarette, that essentially none of these substances is taken into the body with the smoke.

The method of incorporating the substances of the present invention into the tobacco is not critical. Any method commonly recognised in the tobacco art for incorporating additives into tobacco, which results in a substantially uniform dispersion of the additive, may be used so long as the conditions are not such as would adversely affect the active substances used in this invention (i.e. excessive heat and prolonged exposure to moisture). The stability characteristics of ascorbic and erythorbic acid and their salts, as well as methods of preventing or retarding the degradation thereof, are well known in the food and pharmaceutical fields. It is preferred to add the active substances used in the present invention to tobacco by blending therewith in the dry state or by applying them as a solution or suspension in a suitable solvent such as water, ethanol, a polyhydric alcohol or the like.

By "pharmaceutically acceptable salts" is meant those salts of ascorbic acid and erythorbic acid with pharmaceutically acceptable inorganic bases such as, for example, the sodium salt, the potassium salt and the calcium salt.

The following Examples illustrate the present invention:

Example 1.

Tobacco removed from commercially prepared cigarettes was treated in the following manner. An aqueous solution containing 75 mg/ml of an equimolar mixture of ascorbic acid and sodium ascorbate was sprayed on to the tobacco. The amount of solution applied was approximately 15% by weight based on the dry weight of the tobacco. The tobacco was then dried using a stream of nitrogen gas until the weight gain of the treated tobacco was equal to the amount of the ascorbic acid/sodium ascorbate mixture deposited (i.e. all the applied water had been removed). The thus-treated tobacco was then weighed to give

the same proportionate fill as that previously recorded for the commercial cigarettes and was then formed into cigarettes. Cigarettes prepared in this manner were approximately 7 cm in length and contained 0.83 grams of tobacco per cigarette.

A total of 15 grams of an equimolar mixture of ascorbic acid and sodium ascorbate was pulverised to a fine powder using a mortar and pestle. A sufficient quantity of this mixture was added to the tobacco taken from commercially prepared cigarettes to represent 3.75% by weight thereof. The ascorbic acid mixture was added in small portions while rotating the mixing vessel, thereby assuring homogeneous distribution. Cigarettes were prepared from this tobacco.

As controls, cigarettes were prepared from tobacco removed from commercial cigarettes which had been sprayed with distilled water and dried using nitrogen gas until the initial weight of the tobacco was achieved.

Example 2.

Cigarettes were prepared in accordance with the first method described in Example 1 using a sufficient amount of an aqueous solution of an equimolar mixture of ascorbic acid and sodium ascorbate so that each cigarette contained a total of 25 mg. The cigarettes of the mixture were smoked in an apparatus similar to that described by Millar *et al*, Cancer Research, Vol. 28, pages 968—971 (1968). The collected tars from treated and untreated control cigarettes were individually analysed for ascorbic acid content. The analytical procedure utilised was that outlined by Roe *et al* "Methods of vitamin assay" third edition, pages 318 ff., Interscience (1966). The results of this analysis are given in the following Table:

TABLE

Sample	µg Ascorbic acid in tars from 20 cigarettes
Untreated cigarettes	20
Untreated cigarettes + 100µg ascorbic acid added for analysis purposes	117
Treated cigarettes	27

The results of the foregoing analysis indicate that a maximum of 1 part in 10,000 of the ascorbic acid content of the tobacco was

carried over into the tar fraction of the smoke. The value of 27 micrograms per 20 cigarettes lies near the limit of detection for ascorbic acid under the analytical conditions used. It is therefore a reasonable assumption that more sensitive methods of testing may reveal that the value of ascorbic acid in the tar may be even lower than shown in the foregoing Table. The results given in the Table can be interpreted as indicating that essentially no ascorbic acid is transferred from the treated tobacco to the tar during the smoking process.

Example 3.

Whatman No. 1 filter paper was cut into discs having a diameter of 13 mm. These discs were treated with an aqueous solution of equimolar concentrations of ascorbic acid and sodium ascorbate in accordance with the procedure described in Example 1 so that the concentration thereof in each disc was 0.6 mg of the combination. Discs treated with distilled water served as controls. Such discs were individually mounted in an adapter which was fitted on to a 5 cm³ gas tight syringe. A 2 cm³ sample of a gaseous mixture containing 10 parts per million of nitrogen dioxide was passed twice through each paper disc. The nitrogen dioxide content of this sample was analysed by the method of Greiss-Saltzman, "Methods of Air Sampling and Analysis", American Public Health Assoc., page 333 (1972). The results of this experiment show that the nitrogen dioxide content of the sample passed through the untreated control disc was approximately equal to that passed through the syringe with no disc at all and the the content of the sample passed through the treated disc was, on the average, approximately 10% of the original content of the sample.

Example 4.

Cigarettes treated with 12 mg/cigarette of an equimolar mixture of ascorbic acid/sodium ascorbate and erythorbic acid/sodium erythorbate in accordance with the aqueous solution method described in Example 1 were smoked in the following manner. A 50 ml syringe was used to draw smoke from a cigarette attached to an adaptor. The smoke was immediately deposited in a collection vessel containing Greiss-Saltzman reagent. The smoke of treated and untreated (control) cigarettes was then analysed for nitrogen dioxide content. A standardised fast draw and slow draw technique was used to smoke the cigarettes. The definitions of these techniques are set forth in the following Table:

TABLE

Parameter	Fast Draw	Slow Draw
Puff volume	35 cm ³	35 cm ³
Puff duration	2 sec	6 sec
Puff frequency	1 min	1 min
Average butt length	23 mm	33 mm

The results of the tests are set forth in the following Table in which the amount of nitrogen dioxide in the smoke is given as a per cent of control.

TABLE

	Slow Draw	Fast Draw
Ascorbic acid & sodium ascorbate	38	58
Erythorbic acid & sodium erythorbate	35	52

Example 5.

Cigarettes prepared in accordance with Example 1 using a sufficient amount of a powder mixture of equimolar amounts of ascorbic acid and sodium ascorbate so that each cigarette contained 35 mg of the mixture were smoked on an apparatus described by Millar *et al*, Cancer Research, Vol. 28, pages 968—971, May, 1968. The tars from treated cigarettes and controls were analysed for N-nitrosamine content according to the method of Rhoades *et al*, Journal of the National Cancer Institute, Vol. 48, pages 1841—1943 and 1845—1847 (1972). The results of this test show that the content of dimethyl - N - nitrosamine of the cigarette smoke in controls was reduced by approximately 70% in the treated cigarettes.

We are aware of the Customs and Excise Act, 1952 and we make no claim to the use of the invention in contravention to the law.

WHAT WE CLAIM IS:—

1. A composition comprising tobacco and, dispersed therein, a substance selected from

a substantially equimolar mixture of ascorbic acid and a pharmaceutically acceptable salt thereof, a substantially equimolar mixture of erythorbic acid and a pharmaceutically acceptable salt thereof and mixtures thereof.

2. A composition according to claim 1, wherein the sodium salt is present as the pharmaceutically acceptable salt of ascorbic acid and of erythorbic acid.

3. A composition according to claim 1 or claim 2, wherein the substance is present in an amount of from 0.1% by weight to 10% by weight of the tobacco.

4. A composition according to claim 3, wherein the substance is present in an amount of from 1% by weight to 4% by weight of the tobacco.

5. A process for the manufacture of compositions based on tobacco, which process comprises dispersing throughout the tobacco a substance selected from a substantially equimolar mixture of ascorbic acid and a pharmaceutically acceptable salt thereof, a substantially equimolar mixture of erythorbic acid and a pharmaceutically acceptable salt thereof and mixtures thereof.

6. A process according to claim 5, wherein the sodium salt is used as the pharmaceutically acceptable salt of ascorbic acid and of erythorbic acid.

7. A process according to claim 5 or claim 6, wherein the substance is used in an amount of from 0.1% by weight to 10% by weight of the tobacco.

8. A process according to claim 7, wherein the substance is used in an amount of from

1% by weight to 4% by weight of the tobacco.

9. A process for the manufacture of compositions as claimed in claim 1, substantially as hereinbefore described with reference to the foregoing Examples.

10. Compositions as claimed in claim 1, when manufactured by the process claimed in any one of claims 5 to 9 inclusive.

11. A method for the reduction of nitrogen dioxide content in tobacco smoke, which method comprises passing said smoke through uncombusted tobacco having dispersed therein an effective amount of a substance selected from a substantially equimolar mixture of ascorbic acid and a pharmaceutically acceptable salt thereof, a substantially equimolar mixture of erythorbic acid and a pharmaceutically acceptable salt thereof and mixtures thereof.

12. A method according to claim 11, wherein the sodium salt is used as the pharmaceutically acceptable salt of ascorbic acid and erythorbic acid.

13. A method according to claim 11 or claim 12, wherein the tobacco contains from 0.1% by weight to 10% by weight of the substance.

14. A method according to claim 13, wherein the tobacco contains from 1% by weight to 4% by weight of the substance.

For the Applicants,
CARPMAELS & RANSFORD,
Chartered Patent Agents,
43, Bloomsbury Square,
London, WC1A 2RA.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1977.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.